CLAIMS

1. A mutated steroid hormone receptor protein, wherein said receptor protein is capable of distinguishing a hormone antagonist from an agonist.

2. The mutated steroid hormone receptor protein of Claim 1, wherein said receptor protein is selected from the group consisting of estrogen, progesterone, glucocorticoid-α, glucocorticoid-β, mineralocorticoid, androgen thyroid hormone, retinoic acid, retinoid X, Vitamin D, COUP-TF, ecdysone, Nurr-1 and orphan receptors.

3. The mutated steroid receptor protein of Claim 1, wherein said protein is mutated by deletion of carboxy terminal amino acids.

4. The mutated steroid hormone receptor protein of Claim 3, wherein said deletion comprises from about 1 to about 120 amino acids.

5. The mutated steroid hormone receptor protein of Claim 3, wherein said protein is mutated by deletion of from about one to about 60 amino acids on the carboxy terminal end of said protein.

6. The mutated steroid hormone receptor protein of Claim 3, wherein said carboxy terminal deletion comprises deletion of 42 amino acids.

7. A plasmid containing the mutated steroid hormone receptor protein of Claim 1.

8. The plasmid of Claim 7, wherein said steroid hormone receptor protein is selected from the group consisting of estrogen, progesterone, glucocorticoid-α, glucocorticoid-β, mineralocorticoid, androgen, thyroid hormone, retinoic acid, retinoid X, Vitamin D, COUP-TF, ecdysone, Nurr-1 and orphan receptors.

9. The plasmid of Claim 7, designated UP-1.

10. The plasmid of Claim 7, wherein said plasmid is selected from the group consisting of YEphPR-A879, YEphPR-A891, YEphPR-B891, YEphPR-B879, phPR-A879, phPR-A891, phPR-B879 and phPR-B891.

11. A transfected cell containing the plasmid of Claim 7.

12. The transfected cell of Claim 11, wherein said cell is selected from the group consisting of yeast, mammalian and insect cells.

13. The transfected cell of Claim 12, wherein said yeast is *Saccharomyces cerevisiae*.

14. The transfected cell of Claim 12, wherein said mammalian cell is selected from the group consisting of HeLa, CV-1, COSM6, HepG2, CHO and Ros 17.2.

15. The transfected cell of Claim 12, wherein said insect cell is selected from the group consisting of SF9, drosophila, butterfly and bee.

16. A transformed cell line containing the plasmid of Claim 7.

17. A transfected cell containing the plasmid of Claim 9.

18. A transformed cell line containing the plasmid of Claim 9.

19. A method of determining antagonist activity of a compound for a mutated steroid hormone receptor, comprising the steps of:

contacting said compound with a transfected cell of Claim 10; and

measuring transcription levels induced by said compound.

20. A method of determining agonist activity of a compound for a mutated steroid hormone receptor comprising the steps of:

contacting said compound with transfected cells of Claim 10; and

measuring transcription levels induced by said compound.

21. The method of Claim 19 or 20, wherein said receptor protein is selected from the group consisting of estrogen, progesterone, glucocorticoid-α, glucocorticoid-β, mineralocorticoid, androgen, thyroid hormone, retinoic acid, retinoid X, Vitamin D, COUP-TF, ecdysone, Nurr-1 and orphan receptors.

22. A method of determining an endogenous ligand for a mutated steroid hormone receptor, comprising the steps of:

contacting a compound with the transfected cells of Claim 11; and

measuring transcription levels induced by said compound.

23. A method of determining an endogenous ligand for a mutated steroid hormone receptor, comprising the steps of:

contacting a compound with the transformed cells of Claim 16; and

measuring transcription levels induced by said compound.

24. A method of determining an endogenous ligand for a mutated steroid hormone receptor, comprising the steps of

contacting a compound with the transfected cells of Claim 17; and

measuring transcription levels induced by said compound.

25. A method of determining an endogenous ligand for a mutated steroid hormone receptor, comprising the steps of:

contacting a compound with the transformed cells of Claim 18; and

measuring transcription levels induced by said compound.

26. An endogenous ligand for a mutated steroid hormone receptor, wherein said ligand is capable of binding the mutated steroid hormone receptor and stimulating transcription in the transfected cells of Claim 11.

27. An endogenous ligand for a mutated steroid hormone receptor, wherein said ligand is capable of binding the mutated steroid hormone receptor and stimulating transcription in the transformed cells of Claim 16.

28. An endogenous ligand for a mutated steroid hormone receptor, wherein said ligand is capable of binding the mutated steroid hormone receptor and stimulating transcription in the transfected cells of Claim 17.

29. An endogenous ligand for a mutated steroid hormone receptor, wherein said ligand is capable of binding the mutated steroid hormone receptor and stimulating transcription in the transformed cells of Claim 18.

30. A mutated progesterone receptor protein, said mutated progesterone receptor having a carboxy terminal deletion of 42 amino acids.

31. A composition of matter comprising plasmid UP-1 containing a mutated steroid hormone receptor.

32. A molecular switch for regulating expression of a nucleic acid cassette in gene therapy, comprising:

a modified steroid receptor, said receptor including a natural steroid receptor DNA binding domain linked to a modified ligand binding domain,

33. The molecular switch of claim 32, wherein the natural steroid receptor DNA binding domain has been replaced with a non-native or modified DNA binding domain.

34. The molecular switch of claim 32 or 33, wherein the ligand binding domain is modified to bind a compound selected from the group consisting of non-natural ligands, anti-hormones and non-native ligands.

35. The molecular switch of claim 32 or 33, wherein the ligand binding domain binds a compound selected from the group consisting of 5-alpha-pregnane-3,2-dione; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-propinyl-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one; 11β-(4-acetylphenyl)-17β-hydroxy-17α-(1-propinyl)-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1(Z)-propenyl-estra-

4,9-diene-3-one;(7β,11β,17β)-11-(4-dimethylaminophenyl)-7-methyl-4',5'-dihydrospiro[ester-4,9-diene-17,2'(3'H)-furan]-3-one; (11β,14β,17α)-4',5'-dihydro-11-(4-dimethylaminophenyl)-[spiroestra-4,9-diene-17,2'(3'H)-furan]-3-one.

36. The molecular switch of claim 32 or 33, wherein the receptor is selected from the group consisting of estrogen, progesterone, androgen, Vitamin D, COUP-TF, cis-retonic acid, Nurr-1, thyroid hormone, mineralocorticoid, glucocorticoid-α, glucocorticoid-β and orphan receptors.

37. The molecular switch of claim 33, wherein the modified steroid receptor is a receptor with the natural DNA binding domain replaced with a DNA binding domain selected from the group consisting of GAL-4 DNA, virus DNA binding site, insect DNA binding site and a non-mammalian DNA binding site.

38. The molecular switch of claim 32 or 33, further comprising linking a transactivation domain selected from the group consisting of VP-16, TAF-1, TAF-2, TAU-1 and TAU-2 to the modified steroid receptor.

39. The molecular switch of claim 32 or 33, wherein the modified receptor is a progesterone receptor with the ligand binding domain replaced with modified ligand binding domain which binds non-natural or non-native ligands.

40. The molecular switch of claim 32 or 33, further comprising a TAF-1 transactivation domain linked to the modified receptor.

41. The molecular switch of claim 32 or 33, wherein the steroid hormone includes an ecdysone ligand binding domain.

42. The molecular switch of claim 41, further comprising a TAF-1 transactivation domain.

43. The molecular switch of claim 32 or 33, wherein said switch is tissue specific.

44. The molecular switch of claim 43, wherein the tissue specificity is determined by adding a transactivation domain which is specific to a given tissue.

45. The molecular switch of claim 43, wherein the tissue specificity is determined by the ligand which binds to the modified steroid hormone receptor.

46. A method for regulating expression of a nucleic acid cassette in gene therapy comprising the step of attaching the molecular switch of claim 32 or 33, to a nucleic acid cassette to form a nucleic acid cassette/molecular switch complex for use in the gene therapy.

47. The method of claim 46 further comprising the step of administering a pharmacological dose of the nucleic acid cassette/molecular switch complex to an animal or human to be treated.

48. The method of claim 47, wherein said molecular switch is turned on or off by dosing the animal or human with a pharmacological dose of a ligand which binds to the modified ligand binding site.

49. A composition of matter comprising a molecular switch linked to a nucleic acid cassette, wherein said cassette/molecular switch complex is positionally and sequentially oriented in a vector such that the nucleic acid in the cassette can be transcribed and when necessary translated in a target cell.

50. A method for regulating nucleic acid cassette expression in gene therapy comprising the steps of:

forming a nucleic acid cassette/molecular switch complex by linking a molecular switch to a nucleic acid cassette in positional relationship such that the expression of the nucleic acid sequence in the nucleic acid cassette is capable of being up-regulated or down-regulated by the molecular switch;

inserting the nucleic acid cassette/molecular switch complex into a cell to form a transformed cell; and

inserting a pharmacological dose of the transformed cell into a human or animal for gene therapy.

51. The method of claim 50 for treating senile dementia or Parkinson's disease, wherein the nucleic acid cassette contains the nucleic

acid sequence coding for a protein selected from the group consisting of a hormone, a neurotransmitter and a growth factor; and the transformed cell is a brain cell.

52. The method of claim 51, further comprising the step of encapsulating the brain cell containing the nucleic acid cassette/molecular switch complex in a permeable structure, said permeable structure capable of allowing the passage of activators of the molecular switch and protein translated from the nucleic acid sequence but preventing passage of attack cells.

53. The method of claim 51 or 52, wherein the molecular switch is comprised of a progesterone receptor with the native ligand binding domain replaced with modified ligand binding domain which binds anti-progesterone.

54. The method of claim 50, 51 or 52 wherein the molecular switch is comprised of a progesterone receptor with the native DNA binding domain replaced with GAL-4 DNA binding domain.

55. The method of claim 50, 51 or 52, wherein the nucleic acid sequence is transcribed to produce a protein after the animal or human is given a pharmacological dose of an anti-progesterone.

56. The method of claim 55, wherein the amount of protein produced in the transformed cell is proportional to the dose of anti-progesterone.

57. The method of claim 53, wherein the molecular switch and a nucleic acid cassette are on separate plasmids and are co-injected into a target cell.

58. The molecular switch of claim 43, further comprising the addition of a tissue-specific cis-element to the target gene.

59. A molecular switch comprised of:

a VP-16 transcription region attached to a modified steroid hormone receptor, said receptor including a GAL-4 DNA binding domain and a modified ligand binding domain.

60. A molecular switch comprised of:

a TAF-1 transcription region attached to a modified steroid hormone receptor, said receptor including a GAL-4 DNA binding domain and a modified ligand binding domain.

61. The molecular switch of claim 59 or 60, wherein the ligand binding domain binds a compound selected from the group consisting of 5-alpha-pregnane-3,2-dione; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-propinyl-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one; 11β-(4-acetylphenyl)-17β-hydroxy-17α-(1-propinyl)-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1(Z)-propenyl-estra-4,9-diene-3-one;(7β,11β,17β)-11-(4-dimethylaminophenyl)-7-methyl-4',5'-dihydrospiro[ester-4,9-diene-17,2'(3'H)-furan]-3-one; (11β,14β,17α)-4',5'-dihydro-11-(4-dimethylaminophenyl)-[spiroestra-4,9-diene-17,2'(3'H)-furan]-3-one.

62. A molecular switch for regulating expression of a nucleic acid cassette in a transgenic animal, comprising:

a modified steroid receptor, said receptor including a natural steroid receptor DNA binding domain linked to a modified ligand binding domain,

63. The molecular switch of claim 62, wherein the natural steroid receptor DNA binding domain has been replaced with a non-native or modified DNA binding domain.

64. The molecular switch of claim 62 or 63, wherein the ligand binding domain is modified to bind a compound selected from the group consisting of non-natural ligands, anti-hormones and non-native ligands.

65. The molecular switch of claim 62 or 63, wherein the ligand binding domain binds a compound selected from the group consisting of 5-alpha-pregnane-3,2-dione; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-propinyl-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one; 11β-(4-

acetylphenyl)-17β-hydroxy-17α-(1-propinyl)-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1(Z)-propenyl-estra-4,9-diene-3-one;(7β,11β,17β)-11-(4-dimethylaminophenyl)-7-methyl-4',5'-dihydrospiro[ester-4,9-diene-17,2'(3'H)-furan]-3-one; (11β,14β,17α)-4',5'-dihydro-11-(4-dimethylaminophenyl)-[spiroestra-4,9-diene-17,2'(3'H)-furan]-3-one.

66. The molecular switch of claim 63, wherein the modified steroid receptor is a receptor with the natural DNA binding domain replaced with a DNA binding domain selected from the group consisting of GAL-4 DNA, virus DNA binding site, insect DNA binding site and a non-mammalian DNA binding site.

67. The molecular switch of claim 62 or 63, further comprising linking a transactivation domain selected from the group consisting of VP-16, TAF-1, TAF-2, TAU-1 and TAU-2 to the modified steroid receptor.

68. The molecular switch of claim 62 or 63, wherein said switch is tissue specific.

69. The molecular switch of claim 68, wherein the tissue specificity is determined by adding a transactivation domain which is specific to a given tissue.

70. The molecular switch of claim 68, wherein the tissue specificity is determined by the ligand which binds to the modified steroid hormone receptor.

71. A method for regulating expression of a nucleic acid cassette in a transgenic animal comprising the step of attaching the molecular switch of claim 62 or 63, to a nucleic acid cassette to form a nucleic acid cassette/molecular switch complex for use in the transgenic animal.

72. The method of claim 71 further comprising the step of administering a pharmacological dose of the nucleic acid cassette/molecular switch complex to the transgenic animal.

73. The method of claim 72, wherein said molecular switch is turned on or off by dosing the transgenic animal with a pharmacological dose of a ligand which binds to the modified ligand binding site.

74. A composition of matter comprising a molecular switch linked to a nucleic acid cassette, wherein the promoter in said cassette/molecular switch complex contains steroid response elements and wherein said cassette/molecular switch complex is positionally and sequentially oriented in a vector such that the nucleic acid in the cassette can be transcribed and when necessary translated in a target cell.

75. A method for regulating nucleic acid cassette expression in a transgenic animal comprising the steps of:

forming a nucleic acid cassette/molecular switch complex by linking a molecular switch to a nucleic acid cassette in positional relationship such that the expression of the nucleic acid sequence in the nucleic acid cassette is capable of being up-regulated or down-regulated by the molecular switch;

inserting the nucleic acid cassette/molecular switch complex into a cell to form a transformed cell; and

inserting a pharmacological dose of the transformed cell into the transgenic animal.

76. The method of claim 75, wherein the molecular switch is comprised of a progesterone receptor with the native DNA binding domain replaced with GAL-4 DNA binding domain.

77. The method of claim 75, wherein the nucleic acid sequence is transcribed to produce a protein after the transgenic animal is given a pharmacological dose of an anti-progesterone.

78. The method of claim 77, wherein the amount of protein produced in the transformed cell is proportional to the dose of anti-progesterone.

79. The method of claim 75, wherein the molecular switch and a nucleic acid cassette are on separate plasmids and are co-injected into a target cell.

80. The molecular switch of claim 68, further comprising the addition of a tissue-specific cis-element to the target gene.

81. The cassette/molecular switch complex of claim 75, further comprising the addition of progesterone responsive elements into a promoter of the cassette/molecular switch complex.

82. A molecular switch for regulating expression of a nucleic acid cassette in a plant, comprising:

a modified steroid receptor, said receptor including a natural steroid receptor DNA binding domain linked to a modified ligand binding domain,

83. The molecular switch of claim 82, wherein the natural steroid receptor DNA binding domain has been replaced with a non-native or modified DNA binding domain.

84. The molecular switch of claim 82 or 83, wherein the ligand binding domain is modified to bind a compound selected from the group consisting of non-natural ligands, anti-hormones and non-native ligands.

85. The molecular switch of claim 82 or 83, wherein the ligand binding domain binds a compound selected from the group consisting of 5-alpha-pregnane-3,2-dione; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-propinyl-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadiene-3-one; 11β-(4-acetylphenyl)-17β-hydroxy-17α-(1-propinyl)-4,9-estradiene-3-one; 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-1(Z)-propenyl-estra-4,9-diene-3-one;(7β,11β,17β)-11-(4-dimethylaminophenyl)-7-methyl-4',5'-dihydrospiro[ester-4,9-diene-17,2'(3'H)-furan]-3-one; (11β,14β,17α)-4',5'-dihydro-11-(4-dimethylaminophenyl)-[spiroestra-4,9-diene-17,2'(3'H)-furan]-3-one.

86. The molecular switch of claim 83, wherein the modified steroid receptor is a receptor with the natural DNA binding domain replaced with a DNA binding domain selected from the group consisting of GAL-4 DNA, virus DNA binding site, insect DNA binding site and a non-mammalian DNA binding site.

87. The molecular switch of claim 82 or 83, further comprising linking a transactivation domain selected from the group consisting of VP-16, TAF-1, TAF-2, TAU-1 and TAU-2 to the modified steroid receptor.

88. The molecular switch of claim 82 or 83, wherein said switch is tissue specific.

89. The molecular switch of claim 88, wherein the tissue specificity is determined by adding a transactivation domain which is specific to a given tissue.

90. The molecular switch of claim 88, wherein the tissue specificity is determined by the ligand which binds to the modified steroid hormone receptor.

91. A method for regulating expression of a nucleic acid cassette in a plant comprising the step of attaching the molecular switch of claim 82 or 83, to a nucleic acid cassette to form a nucleic acid cassette/molecular switch complex for use in the plant.

92. The method of claim 91 further comprising the step of administering a pharmacological dose of the nucleic acid cassette/molecular switch complex to the plant.

93. The method of claim 92, wherein said molecular switch is turned on or off by dosing the plant with a pharmacological dose of a ligand which binds to the modified ligand binding site.

94. A method for regulating nucleic acid cassette expression in a plant comprising the steps of:

forming a nucleic acid cassette/molecular switch complex by linking a molecular switch to a nucleic acid cassette in positional relationship such that the expression of the nucleic acid sequence in

the nucleic acid cassette is capable of being up-regulated or down-regulated by the molecular switch;

inserting the nucleic acid cassette/molecular switch complex into a cell to form a transformed cell; and

inserting a pharmacological dose of the transformed cell into the plant.

95. The method of claim 94, wherein the molecular switch is comprised of a progesterone receptor with the native DNA binding domain replaced with GAL-4 DNA binding domain.

96. The method of claim 94, wherein the nucleic acid sequence is transcribed to produce a protein after the plant is given a pharmacological dose of an anti-progesterone.

97. The method of claim 96, wherein the amount of protein produced in the transformed cell is proportional to the dose of anti-progesterone.

98. The method of claim 94, wherein the molecular switch and a nucleic acid cassette are on separate plasmids and are co-injected into a target cell.

99. The cassette/molecular switch complex of claim 94, further comprising the addition of progesterone responsive elements into a promoter of the cassette/molecular switch complex.

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